

### **REMARKS**

Claims 1, 3-10, and 16-23 were previously pending and under consideration by the Examiner in this Application. Claims 2 and 11-15 were previously canceled. Claims 7-9 and 19-23 are presently canceled, and claims 24-27 are newly added by this Amendment. Claims 1, 3-6, 10, and 16-18 are currently amended. Support for the inclusion of Mn and Mo in claims 10 and 27 can be found on page 6, line 20, of the Application as originally filed. Applicant submits that no new matter has been added to the Application by this Amendment.

Each of the rejections levied in the outstanding Office Action is addressed individually below.

#### *Interview Summary*

Applicants thank Examiners Ali Soroush and Karlheinz Skowronek for the telephonic interview of January 10, 2010. During the interview, the outstanding rejections and cited art were discussed.

#### *Rejection under 35 U.S.C. § 103*

Claims 1, 3-10, and 16-23 remain rejected by the Examiner under 35 USC § 103(a) as being obvious over Oeltgen *et al.*, U.S. 6,645,938 ("Oeltgen"), in view of Motterlini *et al.*, *Circ. Res.*, 2002, 90, e17-e24 ("Motterlini").

Without seeming to agree with the Examiner's argument, and solely to facilitate the prosecution of the present Application, Applicant has amended the claims to recite specific carbon monoxide-releasing metal carbonyl compounds of the formula  $M(CO)_x A_y B_z$ .

The experimental results using the recited metal carbonyl compounds are summarized on pages 17-18 and represented by Figures 1-4. These results support the surprising finding that the currently claimed methods, comprising metal carbonyl compounds of the formula  $M(CO)_x A_y B_z$ , as exemplified by CORM-3, promote the functional recovery of hearts subjected to ischemia-reperfusion. As shown in Figures 2A, 2B, and 2C, the cardiac performance of hearts treated with CORM-3 at reperfusion was higher compared to control hearts. As shown in Figures 3A and 3B, CORM-3 was also capable of preventing the increases in end diastolic pressure (EDP) and coronary

perfusion pressure (CPP) that are typical of post-ischemic myocardial dysfunction. As shown in Figure 4A, biochemical and histological analysis confirmed the beneficial effect of CORM-3 in ameliorating the functional recovery of the ischemic hearts. Creatine kinase (CK) activity, an index of cardiac tissue injury, was elevated in the buffer of reperfused control hearts, but the activity was attenuated in the presence of CORM-3. Similarly, the infarct size measured by staining the myocardial tissue with tetrazolium red at the end of the reperfusion period was reduced in hearts reperfused with CORM-3 compared to control (Figures 4B and 4C). Thus, the currently claimed methods comprising metal carbonyl compounds of the formula  $M(CO)_x A_y B_z$  are supported by the experimental results provided in the application.

Applicant respectfully submits that the cited art does not render obvious the use of the metal carbonyl compounds of the formula  $M(CO)_x A_y B_z$ , recited in the present claims, for the treatment of organs, because the cited references do not teach or suggest the compounds recited in the claims.

As described in our previous response of June 7, 2010, Oeltgen teaches methods of preventing damage to isolated organs by exposing the organs to a preservative solution containing an effective amount of a peptide which does *not* release carbon monoxide (CO). The Examiner admits that Oeltgen does not teach a preservative solution containing a metal carbonyl compound which releases CO.

The Examiner alleges that the deficiencies in Oeltgen are cured by Motterlini, which teaches metal carbonyl compounds that release CO. Motterlini further teaches that CO is produced enzymatically in the body by heme oxygenase (*e.g.*, HO-1), and “represents a pivotal inducible defensive system against stressful stimuli, including ... ischemia-reperfusion damage ...” The Examiner concluded that the claimed invention is obvious in view of Motterlini’s teachings that CO generated by HO-1 can defend against ischemia-reperfusion damage and that CO is alternatively generated by the metal carbonyl compounds disclosed by Motterlini. However, Motterlini does not teach or suggest metal carbonyl compounds of the formula  $M(CO)_x A_y B_z$ , as recited in the present claims. Thus, the currently claimed methods of treating organs with carbon monoxide-releasing metal carbonyl compounds comprising ligand A selected from one of the twenty amino acids,  $O(CH_2COO)_2$ , and  $NH(CH_2COO)_2$  are not taught or suggested by Oeltgen and Motterlini.

The Examiner alleged during the telephonic interview of January 10, 2011, that Ioganson *Russian Chemical Reviews* 1985 54(3):277-292 ("Ioganson") cures the deficiencies in Oeltgen and Motterlini. Ioganson is a 1985 review article that surveys the synthetic methods and chemical reactivity of transition metal compounds comprising amino acid ligands. However, Ioganson does not teach or suggest using such compounds with amino acid ligands *in vivo* to release CO. Without such a teaching, the Examiner has failed to establish a *prima facie* case of obviousness. Further, there is no expectation of success based on the cited art.

Applicant respectfully submits that there is nothing in the combination of cited references which would lead one of ordinary skill in the art to recognize that the metal carbonyl compounds recited in the amended claims of the present Application would be useful to treat organs. Applicant therefore respectfully submits that the prior art does not render obvious the use of the metal carbonyl compounds of the formula  $M(CO)_x A_y B_z$ , recited in the present claims, for the treatment of organs.

In view of the lack of any teaching or suggesting of successfully using the recited metal carbonyl compounds for treating organs, it would not have been obvious to one of ordinary skill in the art to practice the currently claimed methods comprising the currently recited compounds. Applicant respectfully requests that the rejection under § 103 be withdrawn.

In view of the above Amendments and Remarks, Applicant believes the pending Application is now in condition for allowance. Please charge any unpaid fees associated with this Response, or credit any overpayments, to our Deposit Account No. 23/2825, under Docket No. H0817.70001US00, from which the undersigned is authorized to draw.

Dated: January 18, 2011

Respectfully submitted,

By \_\_\_\_\_/Kevin M. Henry/\_\_\_\_\_  
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